Persistent and progressive long-term lung disease in survivors of preterm birth.

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SUMMARY

Preterm birth accounts for approximately 11% of births globally, with rates increasing across many countries. Concurrent advances in neonatal care have led to increased survival of infants of lower gestational age (GA). However, infants born <32 weeks of GA experience adverse respiratory outcomes, manifesting with increased respiratory symptoms, hospitalisation and health care utilisation into early childhood. The development of bronchopulmonary dysplasia (BPD) – the chronic lung disease of prematurity – further increases the risk of poor respiratory outcomes throughout childhood, into adolescence and adulthood. Indeed, survivors of preterm birth have shown increased respiratory symptoms, altered lung structure, persistent and even declining lung function throughout childhood. The mechanisms behind this persistent and sometimes progressive lung disease are unclear, and the implications place those born preterm at increased risk of respiratory morbidity into adulthood. This review aims to summarise what is known about the long-term pulmonary outcomes of contemporary preterm birth, examine the possible mechanisms of long-term respiratory morbidity in those born preterm and discuss addressing the unknowns and potentials for targeted treatments.

PRETERM BIRTH AND CHRONIC LUNG DISEASE IN THE NICU

Prematurity is associated with adverse neonatal outcomes, particularly respiratory outcomes as a result of interrupted lung development [1]. Very premature infants are particularly vulnerable as they are born during the canalicular (16–26 weeks GA) and saccular (26–36 weeks GA) stages of lung development [2] and consequently forced to exchange gas with an immature lung, with lung development occurring in a relatively hyperoxic *ex utero*environment compared to the *in utero* milieu [1].

The chronic lung disease of prematurity, bronchopulmonary dysplasia (BPD), was first described over 50 years ago in infants with an average gestational age (GA) of 34 weeks (w) and prolonged

exposure to high oxygen concentrations [3]. Significant improvements in neonatal critical care – including routine use of surfactant therapy – occurred during the 1990s [4], such that approximately half of babies born at 25 w GA now survive in high-middle income countries [5]. Consequently, the clinical and pathological characteristics of prematurity and BPD have changed profoundly. "New" BPD is defined as the requirement for supplemental oxygen for at least 28 days, and is characterised by fewer and larger alveoli, decreased pulmonary vasculature, inflammation and variable smooth muscle hyperplasia[6]. Prenatal factors such as *in utero* inflammation [7], intrauterine growth restriction [8], maternal smoking [9], male sex [10], Caucasian race [11] and genetic factors [12] increase the risk of poor respiratory outcomes and BPD (Figure 1). Lower gestational age [13] and longer mechanical ventilation are associated with supplemental oxygen duration and therefore more severe BPD [13]. Postnatal pulmonary inflammation and oxidative stress play a key role in the pathogenesis of BPD [7], [14] and are discussed in more detail in the context of initiating a pathological process that may indeed persist beyond the neonatal intensive care unit (NICU).

Inflammation in the neonatal period

Pro-inflammatory cytokines, adhesion molecules, selectins, and chemokines are found in high levels in infants with BPD and are associated with endothelial interactions leading to decreased vascularisation and simplified alveoli [7]. The inflammatory pathway involved in BPD can be initiated in the prenatal period, for example chorioamnionitis (inflammation of the foetal membranes) elicits a pulmonary inflammatory response in the neonate [7]. Inflammation is then exacerbated by neonatal events including supplemental oxygen therapy, prolonged mechanical ventilation and pulmonary and systemic infections following preterm birth, which decrease alveolar number, internal lung surface area and in turn, lung function [15], [16], [17].

Oxidative stress in the neonatal period

Oxidative stress results from the production of reactive oxygen species (ROS) exceeding the capacity of antioxidant defences [18]. Preterm infants are often supplemented with oxygen at high concentrations to ensure adequate tissue oxygenation, which can produce ROS, particularly in the presence of inflammation in the lung [14]. Subsequent lung injury is of particular consequence to preterm infants, who have decreased intracellular antioxidant defences, such as reduced levels of superoxide dismutase and catalase, compared to term infants [14]. Additionally, many preterm neonates have detectable free iron in their airway surface liquid, which is associated with increased

risk of oxidative injury [19] due to the production of toxic hydroxyl radicals [14]. Several studies observe associations between high levels of oxidative stress markers – including *o*-tyrosine, superoxide proteinases, uric acid, ascorbic acid, surfactant lipid peroxidation and hydroxyl radicals – with prematurity and greater risk of BPD [20], [21].

Interplay between inflammation, oxidative stress and lung injury in prematurity

During pulmonary inflammation, activated neutrophils release ROS, which functionally deactivate protease inhibitors, leading to excess proteases [22], which may contribute to BPD pathogenesis [7]. The release of ROS not only favours tissue damage, but increases capillary permeability, facilitating the passage of cytokines and contributing to a further increase in inflammation [23]. In this way, inflammation and oxidative stress occur in a complex simultaneous and circular manner. Inflammation-induced oxidative stress is evident in infants with BPD, whose alveolar macrophages produce larger amounts of hydrogen peroxide than controls [24].

In summary, pulmonary inflammation and oxidative stress play a key role in lung injury and BPD pathogenesis. We hypothesise that consequences of these factors may persist beyond the neonatal period and contribute to the poor long-term respiratory outcomes seen in survivors of preterm birth. Certainly, as the oldest survivors of this "New" BPD reach their 20 s, it is becoming clear that survivors of preterm birth are at increased risk of significant and ongoing respiratory disease [25].

BEYOND THE NICU

Structural abnormalities

Most of the evidence underpinning our current understanding of the developmental and structural abnormalities of the lung in BPD come from histopathology studies of a few fatal cases in infants; with only one case described beyond 3 years of age [26]. These studies describe simplified alveoli, decreased vasculature and variable smooth muscle hyperplasiain BPD, and all suggest a delay in alveolar development in survivors of prematurity. Animal models of 'new' BPD describe decreased alveolar septation and hyperplasia [27], enlarged and simplified alveoli and increased pulmonary fibrosis, which worsen over time [28]. These are associated with abnormal lung mechanics [29] and shortened life-span [30]. These findings suggest that arrested development and insults to the lung in the neonatal period can result in long-term function-limiting structural alterations.

Indeed, computed tomography (CT) scans from preterm infants and children born in the surfactant era show high rates of structural abnormalities with the presence of bronchial wall thickening (suggesting inflammation or post-inflammatory changes), linear and triangular sub-pleural opacities (likely scarring) and decreased pulmonary attenuation with limited amounts of emphysema detected [31], [32]. Similar findings of sub-pleural opacities were found in several cross-sectional studies at school age [33], [34], [35], with emphysema, bronchial wall thickening and fibrosis also noted [33], [36]. More severe structural lung disease is associated with increased BPD severity and poorer lung function outcomes [31], [32], [34], [35]. Mixed patterns of reduced lung attenuation, bronchial wall thickening and inverse bronchopulmonary artery diameter ratios have also been observed in preterm-born adults [37], with one study of young adult survivors of severe "old" BPD reporting an 84% incidence of emphysema, which correlated with lower FEV_1 values [38]. As no longitudinal CT imaging studies have been performed, it remains unknown whether the decreased pulmonary attenuation seen during mid-childhood resolves, persists or progresses to the emphysema observed in young adults.

In contrast to the results noted by chest CT, the helium-3 magnetic resonance (^{3}HeMR) imaging technique, which assesses alveolar dimensions and uniformity, has shown normalisation after preterm birth [39]. Despite lower FEV_1 values in preterm-born children, alveolar dimensions were not different to term-born children; possibly suggesting catch-up alveolarisation in preterm-born children [39].

Ongoing respiratory morbidity

Beyond the neonatal period, survivors of prematurity experience persistent respiratory symptoms. In the first years of life, preterm-born infants experience more wheeze, use inhaled medications and are re-hospitalised more frequently than their term-born counterparts [40]. Approximately 50% of those with BPD are re-hospitalised in the first year [41]. At school age, preterm-born children are up to 5 times more at risk of wheezing disorders than their term born counterparts [42], and commonly report respiratory symptoms independent of a neonatal diagnosis of BPD [43]. Additionally, preterm children are more likely to have exercise-induced respiratory symptoms, be diagnosed with asthma and are twice as likely to be prescribed inhaler medications, including inhaled corticosteroids (ICS), than term born children [44], [45].

The burden of respiratory disease likely persists beyond childhood with adolescents from a large Swedish cohort (born in the late-preterm period) reporting more wheeze than their term counterparts [46]. Conversely, young adults born preterm from a small study by Landry et al. reported no differences in respiratory symptoms compared to those born at term [47]. Adult survivors of 'old' BPD report increased symptoms, with much higher rates of wheeze and asthma medication use than full-term controls [48].

Although cross-sectional studies generally show increased rates of respiratory symptoms in those born preterm compared to those born at term, longitudinal data describing how these symptoms change over time are lacking. In extremely preterm children, prevalence of respiratory symptoms, hospitalisation and medication use is reported to significantly decrease between 2 and 6 years of age, although high rates of chest deformities at 6 years suggest ongoing respiratory morbidity [49]. Simpson et al. showed that in children born at less than 32 weeks of gestation, rates of wheeze, cough and asthma medication use remained consistent between early and mid-childhood [50]. As the oldest survivors of prematurity in the post-surfactant era are only now reaching early adulthood, more adequately powered studies are needed to establish the prevalence and characteristics of respiratory symptoms, and the consequences of 'new' BPD throughout life.

Impaired lung function

Respiratory symptoms are often reported in the presence of lung function abnormalities in preterm children and lung function is further decreased in children with BPD [25]. Cross-sectional studies report obstructive lung disease throughout childhood and into adulthood with abnormal spirometry parameters in preterm children – namely lower forced expiratory volumes in 1 s (FEV_1), lower forced mid-expiratory flow (FEF_{25-75}) with normal forced vital capacities [33], [36], [43], [44], [45], [46], [47], [51], [52], [53], [54], [55]. Airway obstruction is partially reversible with bronchodilators in about one third of preterm-born infants [56], with studies reporting between 25% and 60% of those with BPD responding to bronchodilators at school age [33], [44], [52], [56]. However, these studies have not reported whether regular, long-term use of bronchodilators is associated with improved lung function outcomes in this population.

Some studies report airway obstruction in the presence of modest restriction [57], [58] with lower lung volumes in preterm infants with and without BPD [59], [60] and reduced residual volume to total lung capacity ratio (RV/TLC) in preterm children at school-age [45] compared to those born at term.

Preterm born children also exhibit altered respiratory mechanics in comparison to term born controls, which is more pronounced in those with BPD, with increased respiratory system resistance and altered elastic properties of the respiratory system (reactance); indicating peripheral lung disease from infancy to at least school-age [33], [36], [44], [61], [62], [63].

There is conflicting evidence of ventilation inhomogeneity in preterm born children using multiple breath washout techniques, with one study reporting elevated inhomogeneity [64] in preterm infants compared to controls, with another detecting no difference [65]. In the mid-childhood extremely preterm EPICure cohort, slightly elevated ventilation inhomogeneity (lung clearance index) was reported in preterm children compared to those born at term [57]yet no differences were seen in a West Australian cohort of similar age [43], although this cohort included children up to 32 weeks of gestational age. Another recent study found that although lung clearance index was not different, the alveolar phase III of washout revealed elevated ventilation inhomogeneity in the conducting airways (Scond) but not the acinarairways (Sacin) of extremely preterm-born children at school age, suggesting a functionally normal alveolar compartment with impaired function of the proximal airways in comparison to controls [66].

Assessments of gas exchange (DL_{CO}) also provide conflicting results, with some studies suggesting decreased alveolar-capillary membrane function in preterm-born children throughout childhood and adolescence [44], [45], [47], [67], while others fail to detect a difference [36], [68]. Those who reported impaired gas exchange assessed cohorts that were born more premature than those who reported no difference, which may account for the inconsistencies between studies. Taken together, it therefore remains unclear whether the alveolar compartment and pulmonary vasculature of preterm-born children develops normally and whether any altered alveolar or pulmonary vascular development is functionally significant in mid-childhood and beyond.

Longitudinal lung function

Few studies have examined longitudinal lung function beyond infancy in survivors of preterm birth, and often in small numbers of participants, of the most extreme neonatal course, prior to routine use of exogenous surfactant and in the absence of all-ages reference equations. Consequently, findings are conflicting.

Across childhood, Filippone et al. showed poor lung function in 17 BPD survivors, which tracked (but did not change trajectory compared to controls) through 2, 9 and 15 years of age [69]. Similarly, no 'catch-up' in lung function from mid-childhood to adolescence was observed in moderate-late preterm-born children with poor lung function [46]. Some studies have documented improvements in FEV_1 *z*-score with individuals born at 33–34 weeks of gestation improving from 8 to 16 years of age [51]. Other studies of preterm children of lower gestational age report significant declines in FEV_1 *z*-scores from childhood to adolescence or young adulthood [70], [71] and more decline in those with BPD or current smoking status [53]. Studies into adulthood report both persistently low [54], [55] and declining [72], [73]lung function in those born preterm in the pre-surfactant era, with one study reporting lung function declines of at least 0.1 *z*-scores per year during childhood in those with BPD (Figure 2) [50].

Consequently, it remains to be established whether lung function deficits in those born preterm track through life or actually worsen over time, especially those born in the era of "new" BPD. Regardless, low 'peak' lung function (FEV_1) and unknown age-related rate of FEV_1 decline during childhood may put ex-preterm children at risk of early onset chronic lung disease in adulthood and early mortality [74]. Additionally, the preterm population are highly susceptible to known predictors of lung function decline, such as increased risk of respiratory infection during early childhood, increased asthma diagnoses and increased airway hyper-responsiveness [74]. Those born preterm may also be subject to other mechanisms of persistent or progressive lung disease that are not influenced by exposures, such as altered growth, genetics, immunity and persistent inflammation and oxidative stress, which are described below.

POSSIBLE MECHANISMS OF PERSISTENT DISEASE

Genetics

Although genetics are known to play a role in the susceptibility of developing BPD [12], it is unknown whether these genetic variances influence the persistence of respiratory morbidity beyond the neonatal period. Because of the multi-factorial nature of the disease, no specific genetic predictors of BPD have been identified, although associations have been made between BPD and altered innate and adaptive immune responses, surfactant metabolism and potential reductions in growth factors like vascular endothelial growth factor (VEGF) [75]. Siezen and colleagues reported increased genetic susceptibility to respiratory syncytial virus (RSV) in preterm-born compared to term-born children, with these differences likely manifested in airway remodelling

and innate immunity such as altered interferon and transforming growth factor-beta (TGF-β) function and altered response to inflammation [76]. This current evidence suggests that genetics may predispose preterm-born individuals to altered immunity, lung repair and lung growth, which can have long-term implications on respiratory health (Figure 3).

Immunity

Normal 'programming' of the immune system occurs *in utero* and throughout the first year of life [77]. Birth prior to term results in incomplete maternal transfer of antibodies (which occurs during the 3rd trimester) to the preterm infant, which may play a role in the increased susceptibility to infection during the first year of life [77]. Prenatal exposures like antenatal glucocorticoids, prenatal infections and inflammation contribute to altered immunity in preterm infants, who have deficiencies in antimicrobial peptides, altered cellular responses to infection [77] and may have a different and unstable microbial colonisation [78]. These early life influences may result in altered immune programming and long-term immune deficiencies [77], putting survivors of preterm birth at risk of increased incidence and severity of respiratory infection, a known risk factor for accelerated lung function decline in adulthood [74].

Inflammation and oxidative stress

Beyond the neonatal period, data to identify and characterise ongoing inflammation and oxidative stress in survivors of preterm birth are limited. Increased levels of chemokines, growth factors, T-helper cytokines (Th-1, Th-2 and Th-17 cytokines) and immunomodulatory mediators have been detected in nasopharyngeal aspirates from preterm infants at 1 year of age [79]. One small study reported that inflammatory markers in exhaled breath condensatedid not differ between school-aged healthy and preterm-born children, although as only a few subjects were studied this finding may lack statistical power [80]. Other studies report increased neutrophilic inflammation, such as a 16-fold increase in sputum neutrophils and a 3-fold increase in sputum IL-8 in 16 children with "old BPD" [81] and increased levels of urinary leukotriene E_4 in children born preterm regardless of BPD diagnosis [82]. It is clear that inflammation is a common underlying process that affects and is affected by predictors of respiratory morbidity like environmental exposures, immune responses, growth factors and genetics. As such, it is likely that inflammation persists in the preterm lung throughout childhood, and must be considered in light of persisting and possibly declining lung function throughout life.

Markers of oxidative stress are abundant in other chronic lung disorders and are linked to ongoing airway inflammation and remodelling [83], however there are limited data in survivors of preterm birth beyond infancy. Filippone et al. reported that adolescents born preterm with and without a history of BPD, had "unexpected" ongoing oxidative stress with increased levels of 8-isoprostane in exhaled breath condensates in the presence of lower lung function when compared to term-born adolescents [84]. The underlying mechanisms of this continuing oxidative stress remain unclear, but the implication that oxidative stress persists through to young adulthood suggests that oxidative damage may play a role in ongoing respiratory morbidity.

Given the integral role of inflammatory and oxidative stress pathways in the pathogenesis of BPD – and their key role in similar respiratory diseases like chronic obstructive pulmonary disease (COPD) – it is an important area for future investigation.

EMERGING TOOLS TO CHARACTERISE LUNG DISEASE

Risk factors for long-term respiratory morbidity are multifactorial and influenced by prenatal, postnatal and childhood events. To examine the complex, multifactorial mechanisms of lung function decline in this vulnerable group more comprehensive, systems biology approaches are needed. 'Omics methods – which include genomics, epigenomics, microbiomics, transcriptomics, proteomics and metabolomics – have been able to distinguish between neonates who go on to develop BPD and those who do not [85]. Beyond infancy, however, only one "omics" investigation has been reported in survivors of preterm birth – a metabolomics study which clearly delineated between the metabolomic profile of exhaled breath condensate in healthy term adolescents and those with BPD [86]. This study suggests differing surfactant lipid profiles, despite the small number of adolescents (all with BPD) exhibiting heterogeneous clinical symptoms and inhaled corticosteroid usage [86]. Although more adequately powered studies are needed, 'omics tools provide a promising approach to better understanding the mechanisms underlying ongoing lung disease in survivors of preterm birth. Importantly, these methods may help to identify potential therapeutic targets and capture the metabolic response to pharmaceutical interventions.

Potential treatments and interventions

Prevention of long-term lung disease in preterm children has been a focus of interventions in the NICU, with the aim of decreasing lung injury. Corticosteroids have anti-inflammatory properties,

with systemic dexamethasone administration in the NICU becoming popular for the prevention of BPD in the 1990s. The respiratory benefits of dexamethasone treatment include decreased ventilator requirements, earlier extubation, improved lung function, decreased lung inflammation, and ultimately improved survival with reduced BPD incidence [87], [88], [89]. However, adverse long term neurodevelopmental effects and increased risk of gastro-intestinal perforation have led to the early termination of some clinical trials and cautious use of postnatal systemic corticosteroids during the neonatal period after preterm birth [90]. Nevertheless, systemic corticosteroids continue to be used especially to aid extubation of chronically ventilator-dependent preterm-born infants [91]. Inhaled corticosteroids (ICS) administered in the neonatal period have not shown effectiveness in preventing BPD [92], and although one recent trial showed no association with adverse neuro-developmental outcome, rates of mortality were higher in neonates who received ICS [93]. Azithromycin, which has been shown to reduce disease severity in other inflammatory lung diseases, may be effective in both the short- and long-term in preterm infants but further studies are needed to determine its efficacy in reducing lung injury in preterm infants [94]. Other potential anti-inflammatory therapies that have shown improvements in respiratory outcomes in animal models include curcumin and mesenchymal stromal celltherapy, but these are yet to be assessed in humans [95].

The benefits of anti-inflammatory treatment in survivors of preterm birth after the neonatal period have been less well studied: in part because the inflammatory contribution to lung disease in survivors of preterm birth remains poorly described. A follow-up at 8–11 years of very preterm children randomised to receive postnatal dexamethasone or placebo in the newborn period demonstrated long-lasting effects of corticosteroid administration, with fewer children exhibiting abnormal spirometry measures in the treated group (40%; $N = 35$) than the placebo group (68%; $N = 28$) [96]. Smaller studies of no more than 18 participants each have shown inconsistent results, with no improvements in lung function or symptoms observed in children aged 7–13 years after ICS; however, a decrease in the variability of the peak expiratory flow was observed [97], [98], suggesting a reduction in bronchial reactivity. One study reported significant improvements in symptoms, lung function and reduced bronchodilator usage in ex-preterm infants aged around 10 months who used ICS [99]. Although there is evidence that ICS may be of some benefit in the preterm population, its clinical use in this population is not clear and larger studies are needed to answer this question. Interventions targeted towards neutrophilic inflammation or those that promote lung growth may be more appropriate considering the phenotype of chronic lung disease after preterm birth.

CONCLUSION

Survivors of preterm birth face a lifetime of respiratory morbidity, with impaired lung structure and function which may worsen over time. It is becoming increasingly clear that not only do prenatal and neonatal events increase the risk of impaired pulmonary function in preterm-born individuals, but exposures through childhood – such as poor growth, infection, inflammation and oxidative stress – may play a larger role than previously thought. Adequately powered systems biology approaches are needed to discern predictors and targets for preventing chronic lung disease after prematurity, due to its complex and multi-factorial nature.

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Figure 1.

Pathophysiology and risk factors for bronchopulmonary dysplasia (BPD). Development of BPD is complex and multifactorial. Inflammation and oxidative stress are associated with many of the risk factors and have been implicated in the pathophysiology of BPD, although the precise mechanisms are not entirely understood. BPD is characterised by altered lung development, with simplified alveoli, potential airway remodelling and a decrease in the growth and maturation of the pulmonary vasculature.

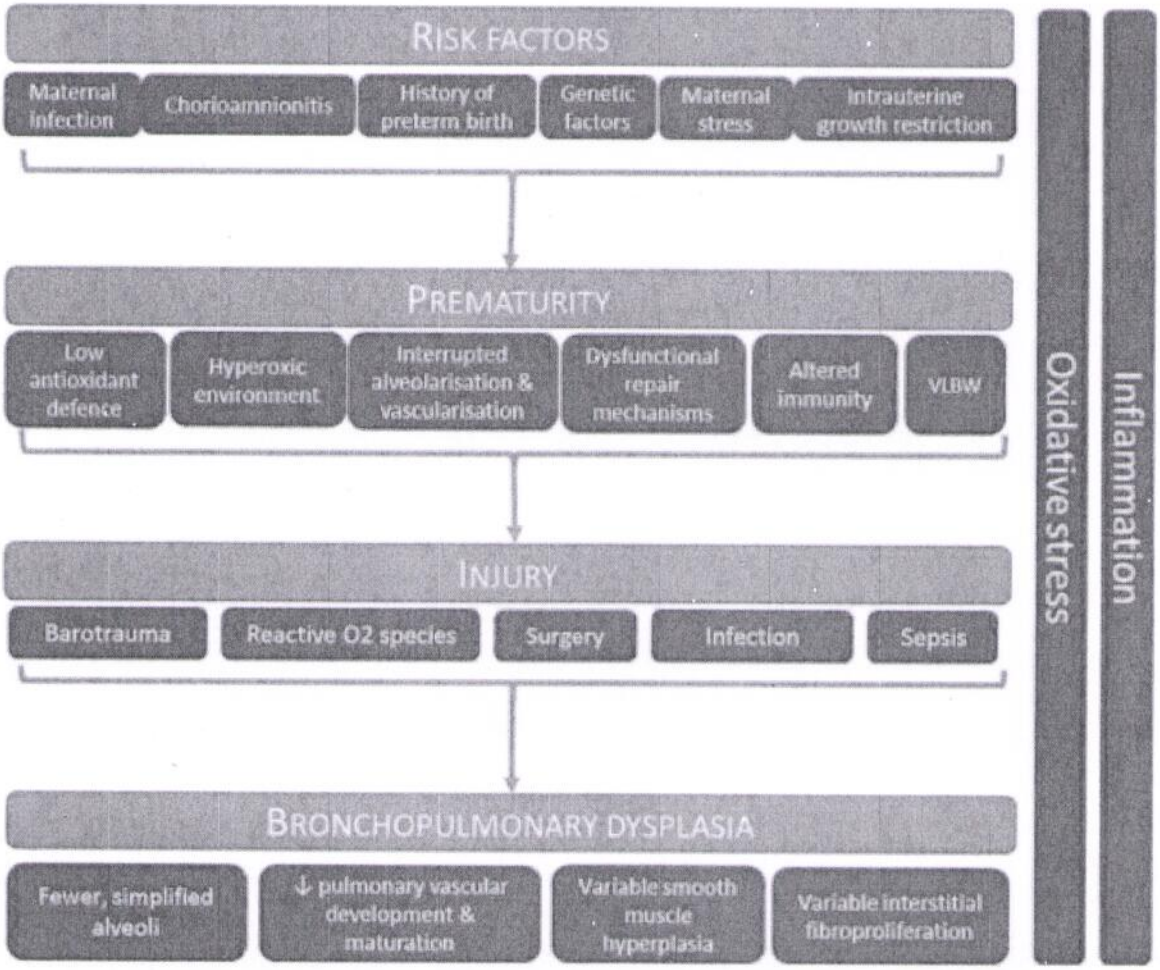

Figure 2.

Longitudinal change in forced expiratory volume in 1 s (FEV_1) over time in children born preterm in the post surfactant era with and without bronchopulmonary dysplasia (BPD). **1.** Simpson et al. report declining lung function trajectories in children born preterm, modelled from 347 lung function visits of children aged 4 to 12 years. FEV_1 declined by a rate of at least 0.1 z-scores per year in children with BPD over the course of the study. **2.** Doyle et al. show increased impairments in airflow from 8 to 18 years of age in survivors of extreme premature birth, which was more pronounced in those with BPD and those smoking at 18 years. **3.** Vollsaeter et al. reported low FEV_1 in extremely preterm children which tracked between 10 and 18 years of age for those with and without BPD. Upper and lower limits of normal are represented by dotted lines. *Indicates significant lung function decline over time relative to a representative population of term-born controls. These studies have shown lung function tracks at z-scores of zero for healthy term-born children. Note: Confidence intervals are not displayed due to inconsistent reporting of results between studies.

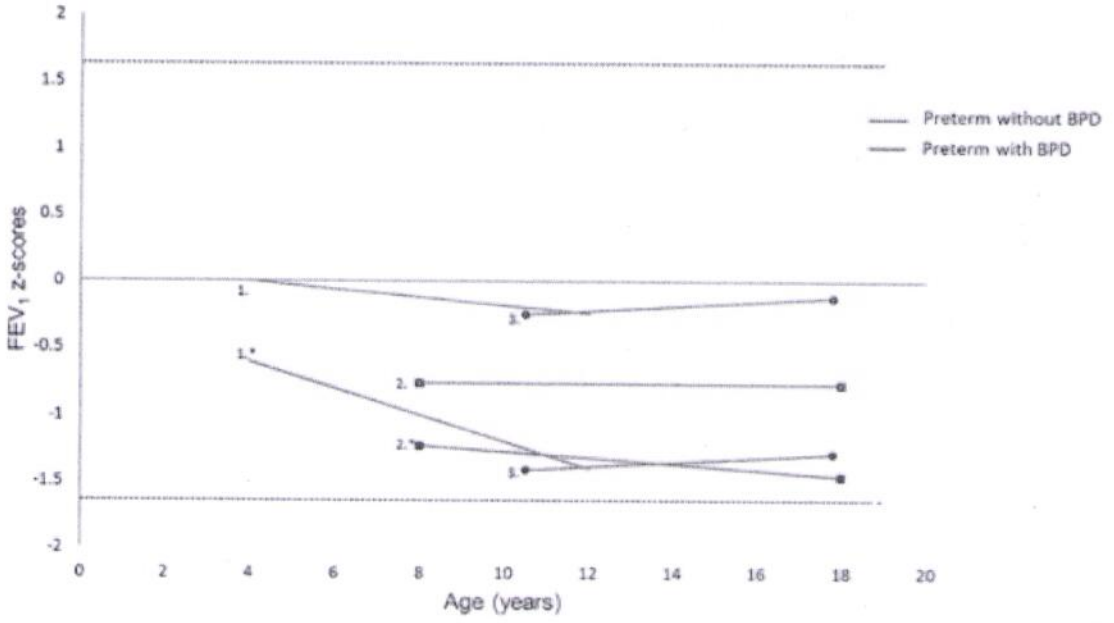

Figure 3.

Proposed risk factors for long-term respiratory morbidity after preterm birth. Survivors of preterm birth are exposed to known risk factors for respiratory morbidity, in addition to genetic factors, altered immunity, impaired lung growth, inflammation and oxidative stress.